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AUTHOR(S):

Fujita, Naotaka; Yamamoto, Yosuke; Hayashino, Yasuaki; Kuwata, Hirohito; Okamura, Shintaro; Iburi, Tadao; Furuya, Miyuki; ... Inagaki, Nobuya; Fukuhara, Shunichi; Diabetes Distress and Care Registry at Tenri Study Group

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Real-life glycemic control in patients with type 2 diabetes treated with insulin therapy: A prospective, longitudinal cohort study (Diabetes Distress and Care Registry at Tenri [DDCRT 9])

Naotaka Fujita^{1,2} , Yosuke Yamamoto¹, Yasuaki Hayashino^{1,3}, Hirohito Kuwata³, Shintaro Okamura³, Tadao Iburi³, Miyuki Furuya³, Masako Kitatani³, Shin Yamazaki¹, Hitoshi Ishii⁴, Satoru Tsujii^{3,*} , Nobuya Inagaki² , Shunichi Fukuhara¹, for the Diabetes Distress and Care Registry at Tenri Study Group

¹Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, ²Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, ³Department of Endocrinology, Tenri Hospital, Tenri, and ⁴Department of Diabetology, Nara Medical University, Kashihara, Nara, Japan

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*Correspondence

Satoru Tsujii
Tel.: +81-743-63-5611
Fax: +81-743-63-1530
E-mail address:
stsujii@tenriyorozyu.jp

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ABSTRACT

Aims/Introduction: We investigated the association between four insulin regimens, and increase in glycated hemoglobin (HbA1c) and insulin dose in a real-life clinical setting because there are no data about them among insulin regimens.

Materials and Methods: Participants included 757 patients with type 2 diabetes having been treated with insulin therapy for more than 1 year. The four insulin regimens were regimen 1 (long-acting insulin, once daily), regimen 2 (biphasic insulin, twice daily), regimen 3 (biphasic insulin, three times daily) and regimen 4 (basal–bolus therapy). Main outcomes were increases in HbA1c levels >0.5% and increases in daily insulin units after 1 year. We carried out multivariable analyses to examine differences in glycemic control and insulin dose with adjustment for possible confounders.

Results: Mean HbA1c level and duration of insulin therapy were 7.8% and 11.3 years, respectively. HbA1c levels increased by >0.5% at follow up in 22.8, 24.9, 20.7, and 29.3% of participants using regimen 1, 2, 3 and 4, respectively, with no significant differences between groups. Daily insulin doses increased in 62.3, 68.8, 65.3 and 38.6% of patients, respectively ($P < 0.001$). Multivariable regression analysis showed that patients who received regimen 4 had significantly lower odds of requiring future insulin dose increases than those who had received regimen 2 (adjusted odds ratio 0.24, 95% confidence interval 0.14–0.41; $P < 0.001$).

Conclusions: Many patients receiving insulin therapy showed increases in HbA1c levels and insulin doses 1 year later. The smallest increase in insulin dose was observed in the basal–bolus therapy group compared with other regimens.

INTRODUCTION

The number of patients with type 2 diabetes is increasing worldwide. In 2015, it was estimated that 415 million people had diabetes, 5.0 million people died from complications of diabetes and up to \$1,197 billion were spent as a result of diabetes

worldwide¹. In high-income countries, type 2 diabetes accounts for >90% of cases of diabetes¹. The main cause of death in patients with type 2 diabetes is cardiovascular disease, but other complications including diabetic nephropathy, retinopathy, and neuropathy can also shorten patients' lives and lower patients' quality of life^{1–4}. The United Kingdom Prospective Diabetes Survey showed that tight glycemic control could decrease

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diabetic complications compared with conventional glycemic control^{5,6}. Glycemic control is as important as blood pressure and lipid control to prevent the occurrence and progression of diabetic complications in patients with type 2 diabetes⁷. Gaede *et al.*⁸ reported that compared with conventional treatment, intensive integrated therapy for hyperglycemia, dyslipidemia and hypertension was effective to reduce cardiovascular events, as well as nephropathy, retinopathy and autonomic neuropathy in approximately half of patients.

In general, when optimal glycemic control is not obtained with dietary therapy and exercise, one or more oral antidiabetic drugs (OADs) is added to the treatment regimen. If sufficient glycemic control is not reached with OADs, insulin therapy is introduced. Recently, glucagon-like peptide-1 receptor agonists have become available as another glucose-lowering agent; these agents can also be combined with OADs. As with OADs alone, when optimal glycemic control is not obtained with glucagon-like peptide-1 receptor agonists and OADs, induction of insulin therapy is recommended^{9,10}.

Many insulin formulations are available, and a variety of insulin regimens have been proposed^{9–11}. Randomized controlled trials suggest an association between a higher frequency of daily insulin injections and greater glycemic improvement in insulin-naïve patients with type 2 diabetes^{12,13}. However, a higher frequency of daily insulin injections is also associated with a higher occurrence of hypoglycemia^{12,13}.

Previous trials observed changes in glycemic control shortly after insulin initiation. It is not clear whether there is a difference in glycemic control among the variety of insulin regimens after their introduction in real-life clinical settings. Thus far, no observational studies have examined practice patterns of glycemic control in patients with type 2 diabetes who have been undergoing insulin therapy for long periods.

Here, we analyzed data of a cohort of Japanese patients with diabetes from a large-scale single-center registry to investigate the association between different methods of insulin therapy in real-life clinical settings and subsequent changes in glycemic control in patients with type 2 diabetes. We also examined factors associated with better glycemic control.

METHODS

Participants

Patient data were derived from the second-year survey of a diabetes registry at Tenri Hospital, Tenri City, Nara, Japan, a regional tertiary-care teaching hospital. Details of this registry can be found elsewhere^{14–21}. In brief, Diabetes Distress and Care Registry at Tenri is a cohort study evaluating the cross-sectional and prospective association among psychosocioeconomic factors, biomedical markers, therapy and complications in patients with diabetes in real-life clinical settings. The registry recruited patients diagnosed with diabetes who had visited the outpatient clinic of our hospital between October 2009 and December 2011. We excluded patients with prediabetes diagnosed by an oral glucose tolerance test, gestational diabetes,

type 1 diabetes, or diabetes induced by steroid use or other endocrinological diseases. We used data only from patients with type 2 diabetes. At registration, the attending physician confirmed the diagnosis according to the Classification and Diagnostic Criteria of Diabetes Mellitus by the Japan Diabetes Society²². For the current analysis, we included patients who had been undergoing insulin therapy with any of the four regimens described later for more than 1 year. Exclusion criteria were renal dysfunction (estimated glomerular filtration rate <15 mL/min/1.73 m²), because it could interfere with the relationship between blood glucose levels and glycated hemoglobin (HbA1c)²³. Patients who started insulin therapy within 1 year were also excluded, because significant changes in HbA1c levels are known to occur within the first year of insulin initiation^{12,13}. Written informed consent was collected from patients. The Ethics Committee of Kyoto University and Tenri Hospital approved this study.

Data collection

On the survey date, patients underwent routine medical history inquiries, physical examinations and laboratory tests. Clinical research coordinators collected the patients' demographics, such as age, sex, bodyweight, height, duration of diabetes and treatment modalities, from their medical charts. With regard to patients undergoing insulin therapy, duration from insulin initiation, daily insulin dose and frequency of self-monitoring of blood glucose were also collected. We assessed patient-reported adherence to scheduled insulin regimens using the response to the following questionnaire: 'How often did you omit insulin injections in the past month?' (response options: 1, never; 2, seldom; 3, less than half of the time; 4, more than half of the time; 5, usually; and 6, always).

Insulin regimens

Main exposures in the present study were one of four insulin regimens: regimen 1 (insulin glargine, once daily), regimen 2 (biphasic insulin, twice daily), regimen 3 (biphasic insulin, three times daily) and regimen 4 (rapid-acting insulin analog, three times daily; and long-acting insulin, once daily), based on the frequency of insulin injection^{9–11}. These specific regimens included the largest number of patients among those receiving one to four insulin injections daily. The rapid-acting insulin analog used was insulin aspart (Novo Rapid[®]; Novo Nordisk, Bagsvaerd, Denmark) or insulin lispro (Humalog[®]; Eli Lilly, Indianapolis, IN, USA) in the present study. Long-acting insulin included neutral protamine Hagedorn (Novolin N[®]; Novo Nordisk), insulin neutral protamine lispro (Humalog N[®]; Eli Lilly), insulin detemir (Levemir[®]; Novo Nordisk) or insulin glargine (Lantus[®]; Sanofi-Aventis, Paris, France). Biphasic insulin included lispro mix 75/25 (75% insulin lispro protamine suspension and 25% of insulin lispro; Eli Lilly), lispro mix 50/50 (50% insulin lispro protamine suspension and 50% of insulin lispro; Eli Lilly) or aspart 30/70 mix (70% protamine-crystallized aspart and 30% soluble insulin aspart; Novo Nordisk).

Outcome measures

The main outcomes were: (i) increase in HbA1c level $>0.5\%$ in 1 year; (ii) increase in insulin dose 1 year later; (iii) addition of OADs in 1 year; and (iv) weight gain in 1 year. HbA1c levels, total daily insulin doses, doses of concomitant OADs, body-weight, and BMI were evaluated at baseline and 12 months after registration in the cohort study. Increases in insulin dose were assessed because these increases are thought to be as important as glycemic control itself, as increasing insulin doses are associated with weight gain and diabetes-related distress²⁴. Excessive weight gain has a harmful effect on lipid levels and blood pressure²⁵, and diabetes-related distress disturbs glycemic control²⁶.

We also evaluated adverse events within 90 days of baseline, such as frequency of hypoglycemia, experience of severe hypoglycemia and frequency of severe hypoglycemia, according to insulin regimen. Hypoglycemia was defined as a case in which a patient felt hypoglycemic symptoms or a case in which measured blood glucose levels were ≤ 50 mg/dL, even if a patient did not feel hypoglycemic symptoms. Severe hypoglycemia was defined as a case in which a patient lost consciousness or a case in which other people's help was required to recover from hypoglycemia.

Statistical analysis

We categorized patients according to insulin regimens. We compared data among the four insulin regimens regarding outcomes; that is: (i) increase in HbA1c level $>0.5\%$ in 1 year; (ii) increase in insulin dose in 1 year later; (iii) addition of OADs in 1 year; and (iv) weight gain in 1 year. Continuous variables are reported as mean \pm standard deviations (SD), and nominal variables are reported as proportions (%). We used analysis of variance to compare continuous variables among the insulin regimens. We also carried out Fisher's exact test for nominal variables.

Then, we used logistic regression analysis to estimate the odds ratios (OR) and 95% confidence intervals (CI) of outcomes (i) and (ii), adjusted for possible confounding factors including age, sex, baseline HbA1c level, duration of diabetes, duration from insulin initiation, presence of OAD use and adherence to insulin therapy. We categorized duration of diabetes into four groups: (i) <10 years; (ii) 10–15 years; (iii) 15–20 years; and (iv) ≥ 20 years. We categorized adherence to insulin therapy into two groups: those who had no experience forgetting an insulin injection (1 = never), and those who had experience forgetting insulin injections (2 = seldom to 6 = always), in order to decrease the deviation in the number of patients. We set regimen 2 as the reference group to make the model most stable, because the largest number of patients were in this group. Also, we carried out sensitivity analysis with an aim to assess the robustness of the primary outcome (i): increase in HbA1c level $>0.5\%$ in 1 year. We changed the cut-off level of an increase of HbA1c >0.5 to 0.1, 0.2, 0.3 and 0.4% in these analyses. For univariate analyses, we used Fisher's exact test for

categorized variables and analysis of variance test for continuous variables. All analyses were carried out using the Stata/SE version 11.2 (StataCorp LP, College Station, Texas, USA). $P < 0.05$ was considered statistically significant.

RESULTS

At baseline, 3,717 patients with type 2 diabetes were registered. Of these 3,717 patients, 1,191 patients (32.0%) without renal dysfunction had been undergoing insulin therapy for more than 1 year. Of these 1,191 patients, 434 patients were excluded because of undergoing insulin therapy with other regimens. Seven hundred and fifty-seven patients with type 2 diabetes were included in the final analysis (Figure 1). Baseline characteristics of patients are shown in Table 1. The mean age was 65.7 years (SD 10.7) and mean HbA1c level was 7.8% (SD 1.2). The mean duration from insulin initiation was 11.3 years (SD 7.7). There were no statistical differences among different insulins within each treatment group (e.g., lispro mix 75/25, lispro mix 50/50 and aspart 30/70 mix in regimen 2).

At baseline, HbA1c level $\leq 6.9\%$ was seen in 26.6, 23.9, 20.4, and 22.9% of patients treated with regimen 1, 2, 3 and 4, respectively. At the end of follow up, HbA1c level $\leq 6.9\%$ was achieved in 27.8, 23.3, 23.4, and 26.8% of patients with regimen 1, 2, 3 and 4, respectively, with no significant differences between groups ($P = 0.76$). The percentage of participants using concomitant OADs was highest in regimen 1 and was lowest in regimen 4. There was no significant association between severe hypoglycemia and insulin regimens in either number of hypoglycemic episodes or the percentage of patients experiencing these episodes ($P = 0.39$ and 0.24, respectively). There was a significant difference in hypoglycemia among the four insulin regimens ($P = 0.005$).

In regimen 4, 14 patients were prescribed neutral protamine Hagedorn, and 69 patients were prescribed insulin analogs (1 insulin neutral protamine lispro, 13 insulin detemir and 54 insulin glargine). There was no significant difference in hypoglycemia between the two groups ($P = 0.30$). The number of severe hypoglycemic episodes or the percentage of patients experiencing these episodes were smaller in patients prescribed insulin analogs (0.071 vs 0.043 times per 90 person days and 7.1 vs 2.9%, respectively), but not significant.

Main outcomes

The percentage of patients whose HbA1c level increased $>0.5\%$ after 1 year were 22.8, 24.9, 20.7, and 29.3% with regimen 1, 2, 3 and 4, respectively, with no significant differences between groups (Table 2). In contrast, daily insulin doses were increased 1 year later in 62.3, 68.8, 65.3, and 38.6% of patients receiving regimen 1, 2, 3 and 4, respectively ($P < 0.001$), whereas no significant differences were observed among regimens in OAD use ($P = 0.37$). Added OADs including classification and dose of medication are shown in Table S1. Weight gain was observed only in regimen 2 ($P = 0.03$). In regimen 4, patients prescribed neutral protamine Hagedorn significantly increased

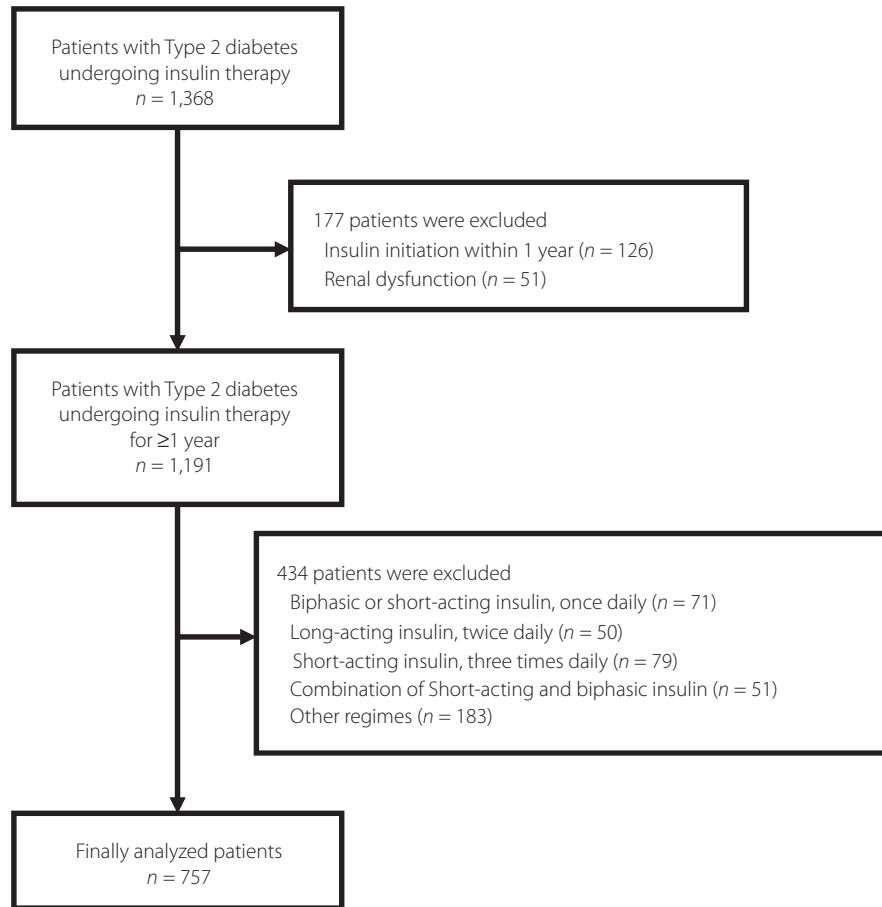


Figure 1 | Selection process for the study population.

Table 1 | Baseline characteristics

	Total (n = 757)	Regimen 1 (n = 79)	Regimen 2 (n = 448)	Regimen 3 (n = 147)	Regimen 4 (n = 83)	P-value
Male (%)	56.1	53.2	55.8	57.8	57.8	0.90
Age (years)	65.7 (10.7)	64.0 (11.8)	67.1 (10.2)	65.4 (8.8)	59.9 (12.7)	<0.001
HbA1c (%)	7.8 (1.2)	7.9 (1.4)	7.8 (1.1)	8.0 (1.2)	7.8 (1.4)	0.17
HbA1c ≤6.9% (%)	23.4	26.6	23.9	20.4	22.9	0.74
Duration of diabetes (years)	17.9 (9.8)	13.4 (10.0)	18.4 (9.8)	18.2 (9.4)	18.4 (9.7)	<0.001
Duration from insulin initiation (year)	11.3 (7.7)	11.0 (9.7)	11.2 (7.2)	12.4 (8.1)	10.6 (7.7)	0.38
Daily insulin dose (unit/kg)	0.43 (0.25)	0.18 (0.09)	0.40 (0.20)	0.49 (0.23)	0.68 (0.34)	<0.001
OAD use (%)	45.3	79.7	45.8	42.2	15.7	<0.001
BMI (kg/m ²)	24.8 (3.8)	24.6 (3.7)	24.8 (3.6)	24.9 (3.9)	25.2 (4.6)	0.62
SMBG (times/day)	1.8 (1.0)	1.2 (0.8)	1.7 (0.9)	2.3 (1.0)	2.2 (1.3)	<0.001
Perfect adherence to insulin therapy (%)	69.9	70.1	71.5	64.6	69.9	0.47
Hypoglycemia (times/90 person days)	2.0 (4.1)	0.4 (1.2)	2.1 (4.5)	2.2 (3.7)	2.4 (4.2)	0.005
Severe hypoglycemia (times/90 person days)	0.021 (0.18)	0 (0.0)	0.024 (0.19)	0.007 (0.08)	0.048 (0.27)	0.39
Severe hypoglycemia (%)	1.86	0	2.24	0.68	3.61	0.24

Data presented as percentage for nominal variables, and mean (standard deviation) for continuous variables. BMI, body mass index; HbA1c, glycated hemoglobin; OAD, oral antidiabetic drug; Regimen 1, long-acting (once daily); Regimen 2, biphasic (twice daily); Regimen 3, biphasic (three times daily); Regimen 4, rapid-acting (three times daily) + long-acting (once daily); SMBG, self-monitoring of blood glucose.

Table 2 | Results of primary outcomes

	Regimen 1 (<i>n</i> = 79)	Regimen 2 (<i>n</i> = 448)	Regimen 3 (<i>n</i> = 147)	Regimen 4 (<i>n</i> = 83)	<i>P</i> -value
HbA1c exacerbation >0.5% (%)	22.8	24.9	20.7	29.3	0.51
Increase in insulin doses (%)	62.3	68.8	65.3	38.6	<0.001
Addition of OAD (%)	30.4	27.7	27.2	19.3	0.37
Weight gain (kg)	−0.29	0.51	−0.23	−0.67	0.03

Data are presented as number (%). *P*-values were determined by Fisher's exact tests for categorized variables and by analysis of variance test for continuous variables. OAD, oral antidiabetic drug; Regimen 1, long-acting (once daily); Regimen 2, biphasic (twice daily); Regimen 3, biphasic (three times daily); Regimen 4, rapid-acting (three times daily) + long-acting (once daily).

Table 3 | Factors associated with glycated hemoglobin exacerbations >0.5% in multivariable analysis

	Adjusted OR	95% CI	<i>P</i> -value
Insulin regimen			
Regimen 1	0.88	(0.48–0.61)	0.68
Regimen 2	Reference	–	–
Regimen 3	0.82	(0.51–1.31)	0.40
Regimen 4	1.05	(0.59–1.87)	0.86
Age (per 10-year increase)	0.76	(0.63–0.91)	0.003
Male (vs female)	0.75	(0.52–1.06)	0.10
Duration of diabetes			
<10 years	Reference	–	–
10–15 years	0.92	(0.55–1.52)	0.74
15–20 years	1.25	(0.76–2.05)	0.39
>20 years	1.63	(1.02–2.60)	0.04
HbA1c at baseline (per 1% increase)	0.68	(0.57–0.80)	<0.001
OAD use (vs no use)	1.10	(0.76–1.60)	0.60
Poor adherence (vs good adherence)	1.33	(0.91–1.94)	0.14

For adjusted odds ratio (OR), confounding factors comprised of age, sex, baseline glycated hemoglobin (HbA1c) levels, duration of diabetes, duration from insulin initiation, presence of oral antidiabetic drug (OAD) use and adherence to insulin therapy were involved. CI, confidence interval; Regimen 1, long-acting (once daily); Regimen 2, biphasic (twice daily); Regimen 3, biphasic (three times daily); Regimen 4, rapid-acting (three times daily) + long-acting (once daily).

bodyweight compared with those prescribed insulin analogs (+1.2 kg vs −1.0 kg, *P* = 0.035).

Multivariable regression analysis showed that there were no statistically significant differences among insulin regimens in increase in HbA1c level >0.5% after 1 year (Table 3). Age (adjusted OR [AOR] 0.76, 95% CI: 0.63–0.91) and higher HbA1c level at baseline (AOR 0.68, 95% CI: 0.57–0.80) were significantly associated with HbA1c exacerbation at the end of follow up. With regard to the relationship between insulin regimens and increase in insulin doses at the end of follow up, multivariable analysis showed that patients who received regimen 4 (AOR 0.24, 95% CI: 0.14–0.41) had significantly lower odds of increasing daily insulin units 1 year later compared with patients who received regimen 2 (Table 4).

Sensitivity analysis

We carried out sensitivity analysis changing the cut-off level of an increase of HbA1c 1 year later to a 0.1, 0.2, 0.3 or 0.4%.

There were no significant differences among insulin regimens in hyperglycemic exacerbations with any cut-off level used (Table 5).

DISCUSSION

The goal of treatment in patients with diabetes is to prevent diabetic complications to extend life expectancy and maintain quality of life. As several longitudinal studies suggest, glycemic control is one of the most important factors in the prevention of diabetic complications^{5–7}. In clinical practice, however, patients and clinicians know the difficulty of maintaining glycemic control²⁷. In the present study, we examined which insulin regimen was better at maintaining glycemic control and not increasing daily insulin doses for patients with type 2 diabetes over an extended period. All four regimens had the same impact on glycemic control, but an increase in insulin dose was less likely in regimen 4 compared with other regimens. In regimen 4, patients prescribed neutral protamine Hagedorn

Table 4 | Factors associated with increase in insulin doses in multivariable analysis

	Adjusted OR	95% CI	P-value
Insulin regimen			
Regimen 1	0.78	(0.46–1.31)	0.34
Regimen 2	Reference	–	–
Regimen 3	0.84	(0.56–1.26)	0.40
Regimen 4	0.24	(0.14–0.41)	<0.001
Age (per 10-year increase)	0.84	(0.71–0.99)	0.04
Male (vs female)	0.97	(0.71–1.33)	0.87
Duration of diabetes			
<10 years	Reference	–	–
10–15 years	0.57	(0.37–0.88)	0.01
15–20 years	0.78	(0.50–1.22)	0.28
>20 years	0.97	(0.63–1.50)	0.89
HbA1c at baseline (per 1% increase)	1.04	(0.91–1.20)	0.54
OAD use (vs no use)	0.96	(0.69–1.34)	0.81
Poor adherence (vs good adherence)	0.96	(0.68–1.34)	0.80

For adjusted odds ratio (OR), confounding factors comprised of age, sex, baseline glycated hemoglobin (HbA1c) levels, duration of diabetes, duration from insulin initiation, presence of oral antidiabetic drug (OAD) use and adherence to insulin therapy were involved. CI, confidence interval; Regimen 1, long-acting (once daily); Regimen 2, biphasic (twice daily); Regimen 3, biphasic (three times daily); Regimen 4, rapid-acting (three times daily) + long-acting (once daily).

Table 5 | Sensitivity analysis

	Regimen 1 (n = 79)	Regimen 2 (n = 448)	Regimen 3 (n = 147)	Regimen 4 (n = 83)	P-value
Increase of HbA1c level					
>0.4% (%)	30.4	31.7	26.9	40.2	0.23
>0.3% (%)	34.2	35.5	33.1	43.9	0.41
>0.2% (%)	40.5	38.9	37.2	47.6	0.46
>0.1% (%)	41.8	42.8	43.6	48.8	0.77

HbA1c, glycated hemoglobin; Regimen 1, long-acting (once daily); Regimen 2, biphasic (twice daily); Regimen 3, biphasic (three times daily); Regimen 4, rapid-acting (three times daily) + long-acting (once daily).

significantly increased bodyweight and tended to experience severe hypoglycemic events compared with those prescribed insulin analogs, which is compatible with another study²⁸.

The present study showed that mean HbA1c levels were approximately 7.8% in all four insulin regimens. In most patients, HbA1c levels were above recommended standards ($\leq 6.9\%$). A target HbA1c level $\leq 6.9\%$ was achieved in just 20–30% of patients in each regimen, although patients continued their insulin therapies for more than 10 years on average. Kobayashi *et al.*²⁹ reported mean HbA1c levels of Japanese patients with type 2 diabetes undergoing insulin therapy was 8.3%, which is even higher than the results in the present study. In the Steno 2 study, HbA1c level $< 6.5\%$ was achieved in just 15% of patients assigned to intensive therapy⁸. These again showed how difficult it is to attain good glycemic control. In addition, HbA1c levels increased by $> 0.5\%$ in $> 20\%$ of patients in all the four insulin regimens, even though these patients were treated in a clinic specializing in diabetes and insulin therapy.

It appears that optimal glycemic control cannot always be obtained even when insulin, the most powerful glucose-lowering agent, is used. This finding could be due to the fact that lifestyle factors, such as diet and exercise, might change with the introduction of insulin. It is also possible that good glycemic control cannot be maintained because of fears of hypoglycemia, as we know simple increasing of insulin dose for poor controlled patients can cause severe hypoglycemia and cardiovascular complication³⁰. As a result, the insulin prescription could be inappropriate to control it despite patients having increased their HbA1c levels during the follow-up period.

When increasing HbA1c levels are seen in patients with diabetes, doctors add OADs or increase insulin doses, as well as reconfirm diet and exercise therapy. In the present study, OADs were added for 20–30% of patients, and insulin doses were increased for 35–70% of patients after 1 year. The insulin dose 1 year later was less likely to increase in regimen 4 compared with the other regimens. In contrast, the occurrence of hypoglycemia was highest with regimen 4 and lowest with

regimen 1. As the frequency of daily injections increased, the occurrence of hypoglycemia also increased, supporting previous studies^{12,13}. We should pay attention to hypoglycemia, because there is a strong association between hypoglycemia and vascular events or decreased quality of life^{31–33}. Although there was a significant difference in hypoglycemia among the four regimens, the occurrence was less than once a month in all regimens, which might be considered clinically acceptable.

We carried out multivariable logistic regression analysis with adjustment for possible confounders. There was no significant difference in the change in HbA1c levels of each regimen compared with regimen 2. In the present study, consistent with another report³⁴, younger patients tended to show worse HbA1c levels compared with elderly patients. In the present study, patients with higher HbA1c at baseline were less likely to show worse HbA1c levels after 1 year. This result might be explained by the fact that a patient with better glycemic control at baseline (e.g., HbA1c $\leq 6.0\%$) remained at fair glycemic control even if HbA1c increased by $>0.5\%$, and the physician might have decided not to add more intervention, because HbA1c levels were still within the target. With regard to the increase in insulin dose, multivariable analysis showed that patients receiving regimen 4 had significantly lower odds of receiving increased insulin doses than patients receiving regimen 2. Insulin doses were unlikely to be increased as a patient aged, which might reflect the fact that doctors hesitated to increase insulin doses in older patients due to fears of hypoglycemia. We changed the cut-off level of an increase in HbA1c $>0.5\%$. Results of sensitivity analysis were also satisfactory after redefining the cut-off level of HbA1c elevation.

There were several limitations to this study. The generalizability of these results is limited, because data are from a single-center, observational study. We adjusted confounding factors in the multivariable analysis, but there remain possibilities that we could not adjust all the confounders including those we did not measure (degree of motivation and adherence to diet and exercise therapy, endogenous insulin secretion, and frequency of educational intervention by medical staff) and other unknown confounders. Furthermore, we cannot exclude the influence of indication bias, because the insulin regimens prescribed to the patients in the present study were based on clinical decisions.

The present study was based on real-world data of 757 patients with type 2 diabetes undergoing insulin therapy for more than 1 year who were treated at an outpatient clinic specializing in diabetes. Regardless of the insulin regimen used, a considerable number of patients treated with insulin therapy showed increases in both HbA1c levels and insulin doses at the end of follow up. These findings indicate the limitations and unmet needs of current insulin regimens. Multivariable regression analysis showed that patients who received regimen 4 had the smallest odds of requiring future insulin dose increases. This might be because a basal-bolus therapy has the largest number of injections, which enables precise and subtle

adjustment of insulin doses supported by and based on results of self-monitoring of blood glucose, with eventually little increase in total daily doses. The current study provides insights on real-life clinical scenarios, and reminds us of the importance of basal-bolus therapy.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Classification and dose of added OADs.